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Editorial

The efficacy of polyunsaturated fatty acids for atherosclerotic diseases

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In the field of anti-aging medicine and health science, various opinions about lipid and health are found. Among lots of clinical and epidemiological research, there has been a significant inverse association between intake of long-chain n-3 polyunsaturated fatty acids (PUFA) and atherosclerosis development [1,2]. These studies included docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and mortality rate with coronary artery diseases. There was also the Japan EPA Lipid Intervention Study (JELIS), which showed the efficacy of reduction of major coronary events [3]. It showed a 19% reduction in major coronary events by a primary endpoint in the EPA group compared with the control group.

Regarding n-3 PUFA, there have been controversies concerning the effect of arteriosclerotic diseases. Formerly, it was rather widely known that the preventive arteriosclerotic effect was present in n-3 PUFA. However, recent papers showed opposite results. This problem is related to not only medical and health matter, but also our meals in our usual lives. In this article, the problem of the effect of n-3 PUFA will be described.

The results of the ASCEND (A Study of Cardiovascular Events iN Diabetes) trial were announced and noted in 2018 [4]. The prevention effect of n-3 PUFA on arteriosclerosis was investigated by Randomized Comparison Test (RCT). The result was negative, which was contrary to the clinical effects previously reported. Formerly, there was a study suggested that fish intake could reduce heart diseases [5]. Later, clinical research has been developed concerning the relationship between lipids and arteriosclerotic diseases such as heart diseases.

Under these circumstances, there are two reports in 2019 from the supreme medical journal, New England Journal of Medicine. Both results were contradictory, in which one showed a preventive effect in REDUCE-IT [6], and another did not show a preventive effect (VITAL) [7]. Details of these reports will be described in the following.

There is a study of the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT). REDUCE-IT was an RCT study from 473 centers in 11 countries [6,8]. The subjects included patients with established cardiovascular diseases or with diabetes and other risk factors, who had been receiving statin therapy with elevated triglyceride and/or LDL-cholesterol level. In other words, the purpose was the check for the prevention of recurrence of arteriosclerotic events. Subjects (n=8,179) were divided into two groups, which

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are EPA group (2 g of EPA twice a day) and control group (mineral oil as placebo), respectively. As a result, the risk of ischemic events was significantly lower in the EPA group. The occurrence was 17.2% vs 22.0% in a primary endpoint event, 11.2% vs 14.8% in secondary endpoint, respectively, indicating the efficacy of the EPA group.

On the other hand, there was a study of Vitamin D and Omega-3 Trial (VITAL) by National Institute of Health (NIH) in the United States [7,9]. It was a randomized, placebo-controlled trial, with a two-by-two factorial design, with vitamin D3 (2000 IU per day) and n-3 fatty acids (EPA 460 mg and DHA 380 mg per day). This investigation was for the primary prevention of cardiovascular disease and cancer in the middle ages. Totally, 25,871 participants were followed up to 5.3 years. As a result, the hazard ratios were in the following: cardiovascular events, 0.93, total myocardial infarction, 0.72, total stroke, 1.04, death from cardiovascular causes, 0.96, death from cancer, 0.97, which are all not with a significant difference. Thus, supplementation with n-3 fatty acids did not show a lower incidence of major cardiovascular events or cancer compared with the placebo.

There are medical papers that examined cardiovascular event inhibitory effects by administering n-3 PUFA. There are ten representative studies concerning the prevention of cardiovascular events reported in 2010-2019. They include I) VITAL, II) REDUCE-IT, III) ASCEND, IV) Age-Related Eye Disease Study 2 (AREDS-2) [10], V) Risk and Prevention Study Collaborative Group (R&P) [11], VI) ORIGIN [12], VII) OMEGA [13], VIII) Alpha Omega Trial Group [14], IX) SU.FOL.OM3 Collaborative Group [15] and X) Diet and Omega-3 Intervention Trial (DOIT) [16].

The reports from I) – III) were already described. The results from IV) – X) were as follows: IV) no reduction in the risk of cardiovascular diseases or secondary cardiovascular outcomes [10], V) daily treatment with n-3 fatty acids did not reduce cardiovascular mortality and morbidity [11], VI) daily supplementation with 1 g of n-3 fatty acids did not reduce the rate of cardiovascular events [12], VII) Low-dose supplementation with EPA-DHA or ALA did not significantly reduce the rate of major cardiovascular events [13], VIII) sudden cardiac death and other clinical events were not reduced by the application of omega-3 fatty acids [14], IX) the result did not support the use of B vitamins or omega 3 fatty acids for prevention of cardiovascular diseases [15], X) there was a tendency toward reduction in all-cause mortality in the n-3 PUFA groups [16].

Among ten reports since 2010, only REDUCE-IT test was the only blinded trial that significantly reduced 3 points major cardiac event (MACE), which was a rather rare case. As regard to myocardial infarction, there is a significant reduction effect in the VITAL. This result can be interpreted that the significance of n-3 PUFA administration has been confirmed by multiple blind tests.

Among previous reports, the important point would be the administered dose of EPA and DHA. There were three trials in which the EPA dose exceeds 1,000 mg/day, JELIS [3], DOIT [16], and REDUCE-IT [6] tests. Among them, the preventive effects of cardiovascular events were found in JELIS and REDUCE-IT [3,6]. In contrast, the preventive effect was not recognized with the smallest amount of DOIT [16]. From mentioned above, it would be considered that the effectiveness may appear when the EPA dose becomes 1,800 mg/day or more in the research protocol.

On the other hand, the content of the placebo is also important. There was no significant effect of suppressing cardiovascular events, when the olive oil was used for the placebo. This is probably because olive oil itself has some efficacy for preventing arteriosclerosis. Meanwhile, mineral oil was used for placebo in the test of REDUCE-IT. The detail element of the placebo was paraffin according to the protocol [6]. Paraffin may be sometimes used as a laxative, and in particular, there are no effects or influences on cardiovascular events. Furthermore, there are other influencing factors such as medicine and lifestyle habits. For LDL-C management, the benefits of administration of statins are proved by abundant evidence recently. It seemed to be the first choice for primary and secondary prevention [17]. There was a study of the risk for developing cardiovascular disease in 11,527 diabetic subjects in the light of diet, exercise, smoking, and alcohol [18]. The hazard ratios of incidence with 3-4 low-risk lifestyle factors were 0.48 for total cardiovascular disease, 0.53 for coronary heart disease, 0.33 for stroke, and 0.32 for cardiovascular mortality ($p < 0.001$) [18].

In summary, it seems difficult to judge whether n-3 PUFA has prevention effect or not for cardiovascular events in various situations. Future research would be expected such as more doses of EPA, combined elements of EPA, DHA, and others, RCT studies and interactions of lifestyle factors.

Conflict of interest

All authors declare that they have no conflict of interest.

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